

**MEMORANDUM: Efficacy Rebuttal**

To: Rita Kumar

From: Autumn Metzger, M.S.

Secondary: Jennifer Urbanski, Ph.D.

Date: 4/28/14

Subject: Response to Rebuttal of Primary Efficacy Review (dated 3/13/2014, DP barcode: 417145)

Product Name: SVP7

EPA Reg. No or File Symbol: 83399-6

Formulation Type: Spot-on

Ingredients statement from the label with PC codes included:

Permethrin, 109701 (36.08%)

Dinotefuran, 044312 (4.95%)

Pyriproxyfen 129032 (0.44%)

**Rebutted claims wanting reconsideration:**

- "Starts killing fleas in 5 minutes on treated dogs"
- "Works fast to kill fleas in 5 minutes on treated dogs"
- "Starts killing new fleas in as little as 5 minutes"
- "kills fleas in 4 hours"
- "kills reinfesting fleas in 4 hours"
- "Starts killing ticks in 1 hour"

**Explanations of the rebuttal grouped by similarity of claims:**

1) Rebuttal claims desired (based on MRID 49262310):

- "Starts killing fleas in 5 minutes on treated dogs"
- "Works fast to kill fleas in 5 minutes on treated dogs"
- "Starts killing new fleas in as little as 5 minutes"

**Rebuttal summary:**

The registrant explains in the rebuttal that by revising the claims to specify "treated dogs" or stating the fleas are "new" indicates that the dogs had been *previously treated over a week earlier*. However, this is not how the consumer may interpret the statements, and it is not what the claims directly state. "Previously" treated means at any previous point in time including "5 minutes previously." The product was not efficacious in 5 minutes from treatment. The company also stated that it is well documented through the testing of fur samples that "generally the product spreads over the whole body within a few hours." However other studies demonstrate that it typically take 48 hours or more to reach the 90% threshold of efficacy after application.

The rebuttal also explains that the study shows 6.5-15.5% of fleas were killed within 5 minutes, however this is not accurate. These numbers represent the total % of *dislodged* fleas which combined dead and moribund fleas. The number of dead fleas found at 5 minutes ranged from 0 -2.8. Counts are as follows:

At 5 minutes:

Day      % of dead fleas

Day 0 = 0

Day 2 = 1.5

Day 7 = 2.8

Day 14 = 1.4

Day 21 = 0.8

Day 28 = 0

These numbers show that not only does the product not kill fleas in 5 minutes at any time point, but that on day 0 at 5 minutes, no fleas were affected at all as there were 0 dead and 0 dislodged fleas.

Claim MRID 49262310 supports the following claim:

- Starts killing new/reinfesting fleas within 1 hour starting 1 day after application

**Any difference from first review: No**

2) Rebuttal claims desired (based on MRID 49262310):

- "kills fleas in 4 hours"
- "kills reinfesting fleas in 4 hours"

Again, the company considers moribund fleas as dead when calculating adult efficacy. On page 25 of the study report it explains that efficacy is calculated using live fleas (therefore including moribund fleas with the dead counts):

Efficacy against fleas was calculated according to the following formula:

Efficacy (%) =  $100 \times (mc - mt) / mc$ , where:

mc = geometric or arithmetic mean of live fleas on the negative control groups (Groups 1A and 1B)

mt = geometric or arithmetic mean of live fleas on the treated groups (Group 2A, 2B, 3A, 3B)

Descriptive statistics (mean, minimum, maximum, standard deviation, CV%, geometric mean and median) on flea counts for the various assessment days were calculated.

Combining moribund and dead ticks in the analysis provides geometric means >90% at each 4 hour time point; however the following table indicates that few fleas actually died by the 4 hour time point (only 1.1 on day 28):

| Collection time point |         | Group 2B - IVP (Vectra 3D®) |          |                   | Group 3B - RVP (Comfortis®) |          |                   |
|-----------------------|---------|-----------------------------|----------|-------------------|-----------------------------|----------|-------------------|
|                       |         | Dead                        | Moribund | Total % dislodged | Dead                        | Moribund | Total % dislodged |
| Day 0                 | 5 min   | 0                           | 0        | 0                 | 0.1                         | 0.4      | 0.5               |
|                       | 10 min  | 0                           | 0        | 0                 | 0                           | 0        | 0.5               |
|                       | 30 min  | 0.1                         | 0.9      | 1.0               | 0                           | 0.4      | 0.9               |
|                       | 4 hours | 18.5                        | 39.1     | 58.6              | 4.4                         | 18.9     | 24.1              |

| Collection time point        |         | Group 2B - IVP (Vectra 3D®) |          |                   | Group 3B - RVP (Comfortis®) |          |                   |
|------------------------------|---------|-----------------------------|----------|-------------------|-----------------------------|----------|-------------------|
|                              |         | Dead                        | Moribund | Total % dislodged | Dead                        | Moribund | Total % dislodged |
| Day +2                       | 5 min   | 3.8                         | 19.1     | 22.9              | 0.3                         | 0.4      | 0.6               |
|                              | 10 min  | 2.4                         | 7.8      | 33.0              | 0                           | 0.8      | 1.4               |
|                              | 30 min  | 7.6                         | 15.9     | 56.5              | 0.4                         | 2.3      | 4.0               |
|                              | 4 hours | 10.8                        | 14.1     | 81.4              | 12.4                        | 14.9     | 31.3              |
| Day +7                       | 5 min   | 1.3                         | 8.6      | 9.9               | 0.6                         | 0.4      | 1.0               |
|                              | 10 min  | 1.1                         | 14.8     | 25.8              | 0.5                         | 0.5      | 2.0               |
|                              | 30 min  | 5.3                         | 18.0     | 49.0              | 1.1                         | 1.0      | 4.1               |
|                              | 4 hours | 7.3                         | 11.8     | 68.0              | 10.0                        | 11.1     | 25.3              |
| Day +14                      | 5 min   | 1.9                         | 9.8      | 11.6              | 0.3                         | 1.1      | 1.4               |
|                              | 10 min  | 0.1                         | 21.9     | 33.6              | 0.9                         | 0.8      | 3.0               |
|                              | 30 min  | 2.4                         | 17.4     | 53.4              | 0.1                         | 0.6      | 3.8               |
|                              | 4 hours | 7.6                         | 7.6      | 68.6              | 6.0                         | 11.8     | 21.5              |
| Day +21                      | 5 min   | 0                           | 6.6      | 6.6               | 0                           | 0.5      | 0.5               |
|                              | 10 min  | 0.1                         | 17.6     | 24.4              | 0                           | 0.4      | 0.9               |
|                              | 30 min  | 1.8                         | 21.4     | 47.5              | 0                           | 0.4      | 1.3               |
|                              | 4 hours | 7.3                         | 11.0     | 65.8              | 3.9                         | 11.3     | 16.4              |
| Day +28                      | 5 min   | 0                           | 12.5     | 12.5              | 0                           | 0.3      | 0.3               |
|                              | 10 min  | 0                           | 13.3     | 25.8              | 0                           | 0        | 0.3               |
|                              | 30 min  | 0.8                         | 26.3     | 52.8              | 0.1                         | 0.1      | 0.5               |
|                              | 4 hours | 1.1                         | 14.6     | 68.5              | 0.6                         | 4.1      | 5.3               |
| Mean total % fleas collected | 5 min   | 12.7                        |          |                   | 0.8                         |          |                   |
|                              | 10 min  | 28.5                        |          |                   | 1.5                         |          |                   |
|                              | 30 min  | 51.8                        |          |                   | 2.7                         |          |                   |
|                              | 4 hours | 70.5                        |          |                   | 19.9                        |          |                   |

<sup>a</sup>Percentage of total number of fleas infested

No new claims are acceptable with this data.

3) Rebuttal claim desired (based on MRID 49262308):

- "Starts killing ticks in 1 hour"

In MRID 49262308, page 23 of the study report reads:



"The arithmetic mean tick counts recorded for Vectra® 3D (Group 2) were statistically significantly ( $p < 0.05$ ) less than that of the untreated control Group 1 from **12 hours post treatment onwards.**"

Therefore, 12 hours post treatment is the earliest time point at which acceptable efficacy is demonstrated for a "starts killing ticks" claim.

The part of the study that counted viability of ticks that were repelled from dogs did not include a statistical analysis at 1 hour on day +1 (page 25). On page 26, the table shows that at this time point the efficacy of repelled ticks was only 1.3% and the viability was 1%.

Claim MRID supports:

- "Starts killing ticks within 12 hours of application"

**Any difference from first review: No**

**Conclusion:**

**None of the requested claims in the rebuttal are acceptable. The claims that were found acceptable in the primary review for the 2 MRIDs rebutted above have not changed. A summary of the acceptable claims, as listed above are:**

- Starts killing new/reinfesting fleas within 1 hour starting 1 day after application
- "Starts killing ticks within 12 hours of application"